REMARKS

Applicants have amended the Specification. The specific changes to the Specification are shown above in the Amendments to the Specification, wherein the insertions are underlined and the ~~deletions are stricken through~~. Applicants have amended Claims 1, 2, 7, 8, 9, 11, and 17, and canceled Claims 10 and 12. Thus, Claims 1-9, 11 and 13-17 are presented for examination. The specific changes to the amended claims are shown above in the Amendments to the Claims, wherein the insertions are underlined and the ~~deletions are stricken through~~. Applicants respond below to rejections made by the Examiner in the Office Action of August 14, 2006.

I. Information Disclosure Statement

Applicants acknowledge and thank the Examiner for the corrections to the IDS.

II. Specification

The Examiner has objected to the disclosure for various informalities. Applicants have responded as follows:

a. Applicants have amended the first sentence of the first paragraph of the specification to indicate that Application 09/798,720 is now U.S. Patent 6,635,424.

b. Applicants have amended the first sentence of the first paragraph to remove the reference to Application No. 07/919,730, and to insert Application No. 07/919,370. The error resulted from the unintentional transposition of two digits – the continuity data of related applications, such as Application No. 07/464,350, include the correct application number, and Applicants thus respectfully submit that the amendment adds no new matter.

c. Applicants have amended the specification on page 7 to indicate that FIG. 4A contains SEQ ID Nos. 1 and 2, and that FIG. 4B contains SEQ ID. Nos. 3 and 7. SEQ ID Nos. 1, 2, and 3 were already included in the Sequence Listing, and thus do not constitute new matter. SEQ ID No. 7 is the amino acid chain of FIG 4B, and thus does not constitute new matter either. Applicants submit herewith Replacement Drawing Sheets and Annotated Marked-up (Redline) Drawings of FIG. 4A and FIG. 4B. Applicants also submit herewith a corrected Sequence Listing in computer readable form pursuant to 37 C.F.R. § 1.821(e) and § 1.825(b). Applicants have also amended the specification on page 38 to add sequence identifiers to the recited amino acid and nucleotide sequences (SEQ ID NOS. 4, 5, and 6); these sequences also already appear in the Sequence Listing, and thus do not constitute new matter.

III. Claim Rejections – 35 U.S.C. § 101

The Examiner has rejected Claims 1-17 under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter. Specifically, the Examiner has alleged that the host cells of the claims have no structural distinction from cells existing in nature. As the Examiner has indicated, recitation of "isolated" host cells would obviate the rejection. Applicants have amended Claims 1 and 9 to recite that the cells are "isolated." Applicants respectfully submit that the amendment overcomes the rejection, and that the dependent claims are patentable for the same reason. Applicants respectfully request withdrawal of the § 101 rejection.

IV. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1-17 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

First, the Examiner alleges that the phrase "DNA comprising genes" is indefinite because "genes" implies a DNA segment that, in addition to containing one or more exon segments, includes leader, trailer, and intron segments, whereas the DNA inserted into a vector does not include the expression control elements that fall under the definition of a gene. Although the claims do not exclude the presence of segments other than exons, Applicants have amended Claims 1, 7, 9, and 17 to remove the references to "genes," and indicate instead that the DNA encodes antibodies or antibody fragments. Applicants respectfully submit that the amendment overcomes the rejection and that the dependant claims are allowable for the same reason.

Next, the Examiner alleges that the phrase "antibody framework vector" is indefinite because the term has divergent meanings in the art. In the context of the present specification, framework vector is a vector that provides a constant region and allows antibody variable regions to be inserted. As the specification states:

> Specifically, a library of genes encoding immunoglobulin heavy chain regions and a library of genes encoding immunoglobulin light chain regions are constructed. This is carried out by obtaining antibody-encoding DNA, which is either genomic fragments or cDNAs of antibody mRNAs, amplfying or cloning the fragments or cDNAs; and introducing them into a ***standard framework antibody gene vector***, which is used to introduce the antibody-encoding DNA into cells in which the DNA is expressed. The vector includes a framework gene encoding a protein, such as a gene encoding an antibody heavy chain or an antibody light chain which

> can be of any origin (human, non-human) and can be derived from any of a number of existing DNAs encoding heavy chain immuno-globulins or light chain immunoglobulins. Such vectors are also a subject of the present invention and are described in greater detail in a subsequent section. Genes from one or both of the libraries are introduced into appropriate host cells, in which the genes are expressed, resulting in production of a wide variety of antigen-combining molecules.

Specification at 4, l. 24 to 5, l. 13 (emphasis added). The specification further teaches at page 14, l. 10 to page 16, l. 2, the construction of a framework vector in which the variable region is deleted, so that a variable region cDNA from a library can be inserted. Accordingly, Applicants respectfully submit that the term framework vector is readily understood by those of skill in the art upon reading the present specification, and submit that the term satisfies the requirements of § 112, second paragraph.

Next, the Examiner has rejected Claims 10 and 11 for the recitation of "said DNA comprises a vector" in Claim 10. Applicants have canceled Claim 10, and amended Claim 11 so that it now depends from Claim 11. Support for expression vectors can be found, for example, in the present specification at page 9, line 27, to page 10, line 29. Applicants respectfully submit that the amendments overcome the rejection.

Applicants respectfully request withdrawal of the § 112, second paragraph rejections.

V. Claim Rejections – 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 1-17 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter lacking written description support in the specification.

First, the Examiner has rejected Claims 1-17, alleging that the specification lacks a description of the "organization, location or actual DNA sequences of promoter and regulatory regions and introns, all defining elements of a "gene." As discussed above, Applicants have amended the claims to remove the recitation of "genes." With regard to the structure and function of the DNA in the framework vector, however, the present specification describes in detail the process of inserting a cloned gene product (in the claim, this is DNA from the library, regardless of whether it contains a complete "gene" or not) into a framework antibody gene vector, including a discussion of particular cloning sites, and by providing relevant background references. *See* page 14, l. 10 to page 15, l. 21. The specification further provides details and background references for inserting a vector into a host cell and expressing antigen-binding

molecules. *See, e.g.*, page 20, l. 15 to page 21, l. 21. One of ordinary skill in the art, upon reading the specification, would thus understand that Applicants were in possession of the invention based on these descriptions of how to construct a library of heavy and light chain sequences, how to insert selected DNA from the library into framework vector, and how to introduce the DNA and the framework vector into a host cell, to the satisfaction of § 112, first paragraph.

The Examiner next rejects Claims 1-17, alleging that the specification lacks a description of a representative number of species of "antigen-combining proteins," which the Examiner has interpreted to include receptors, ligands, kinases, and phosphotases, in addition to antibodies. Applicants have amended Claim 1 so that it no longer recites "antigen-combining protein," and instead recites "antibody or antibody fragment." As the Examiner has indicated, the written description in this case sets forth antibodies and antibody fragments capable of binding an antigen. Applicants respectfully submit that this amendment overcomes the rejection. Claim 9 and its dependent claims already recite "antibodies," rather than "antigen-combining proteins."

The Examiner next rejects Claims 2 and 12, alleging that the specification, while being enabling for prokaryotic host cells producing antibody fragments, does not reasonably provide enablement for the expression of whole immunoglobulins in a prokaryotic cell. Applicants have amended Claim 2 to recite that "the host cell is a prokaryotic host cell producing an antibody fragment." Claim 12 has been canceled. Applicants respectfully submit that the amendments overcome the rejection.

Applicants respectfully request withdrawal of the § 112, first paragraph rejections.

VI. Priority

The Examiner alleges that Applicants' priority claim to January 11, 1990 does not comply with 37 CFR § 1.78(a) because Application 08/997,195 was abandoned on August 13, 1999, and was therefore not copending with Application 09/439,732, filed on November 12, 1999. On September 29, 2006, Applicants filed a Petition to Revive Application 08/997,195 because abandonment on August 13, 1999 was unintentional. Applicants' Petition to Revive was submitted with a Petition to Expedite. However, a January 9, 2007 entry in the transaction history of Application 08/997,195 indicates that the file is marked lost; the case therefore remains unassigned for purposes of considering the Petition to Revive. It is Applicants' understanding

that consideration of the Petition can proceed once the file is found, or in the alternative, if the file is not found, the file can be reconstructed to allow the Petition to be considered. If Applicants' Petition is granted, the priority claim of the present application to January 11, 1990 will comply with the requirements of 37 CFR § 1.78(a). Applicants thus respectfully request the Examiner consider all other outstanding issues in the present application while awaiting a decision with respect to Applicants' Petition to Revive.

VII. Claim Rejections – 35 U.S.C. § 102

The Examiner has rejected Claims 1-17 under 35 U.S.C. § 102(b) as allegedly being anticipated by various references as discussed below.

The Examiner has rejected Claims 1, 3-11, and 13-17 under 35 U.S.C. § 102(b) as allegedly being anticipated by Morrison et al. (PNAS, 81:6851-6855, November 1984). Morrison et al. teach the use of cloned genes (S107 V_H and S107 V_K) encoding the heavy and light chains of a single antibody. As amended, the claims require "selecting from a library DNA encoding ..." Support for this amendment can be found throughout the specification. For example, two types of libraries of DNA, one encoding heavy chains, and one encoding light chains, are discussed at page 4, l. 24 to page 5, l. 13. As taught in the specification, "[g]enes from one or both of the libraries are introduced into appropriate host cells, in which the genes are expressed, resulting in production of a wide variety of antigen-combining molecules." Page 5, ll. 10-13. Additional details regarding such libraries are provided at page 9, l. 1 to page 14, l. 8. The DNA used in Morrison et al. to encode the variable regions of the antibody was not selected from a library - the reference contains no discussion of creating or maintaining a library, or making any other antibodies. Rather, as indicated in Morrison et al., the DNA used was a gift from another institution. *See* Morrison et al. at 6851, first column, first paragraph. By failing to disclose a library of DNA, or selecting particular DNA from such a library, Morrison et al. do not teach or fairly suggest all of the limitations of the invention as claimed, and do not permit the production of a wide variety of antigen-combining molecules.

The Examiner has also rejected Claims 2 and 12 under 35 U.S.C. § 102(b) as allegedly being anticipated by Skerra et al. (Science 240:1038-1041, 20 May 1988). Skerra et al. describe a study conducted to determine whether an F_v fragment of antibody McPC603 made with an E. coli host cell would be functional. *See* Abstract. The fragment created in Skerra et al. is not the

product of inserting DNA into an framework antibody vector, however. Rather, it is the expression only of the nucleotide sequences that encode the heavy and light chains of the variable region of the antibody. *See* page 1039, col. 3. As shown in FIG. 1, the assembled plasmid contains the inserted V_H and V_L (variable) regions, but contains no antibody framework, which is why the resulting protein is only the Fv fragment. That the expression of the protein was conducted in E. coli, a prokaryotic host, does not address the absence of a library from which DNA is selected, as the present claims now require, or the absence of inserting DNA into a framework antibody vector. Thus Skerra et al. do not teach or fairly suggest all of the limitations of the presently claimed invention. Claim 12 has been canceled, but Applicants respectfully submit that Claim 2 is patentable for the reasons discussed above.

The Examiner has also rejected Claims 2 and 12 under 35 U.S.C. § 102(b) as allegedly being anticipated by Better et al. (Science 240:1041-1043, 20 May 1988). Better et al. describe the production of a mouse-human chimeric F_{ab} fragment of an anti C3347 antibody. *See* Abstract. Like Skerra et al., however, the protein fragment is prepared by merely inserting the nucleotide sequence encoding the fragment into a standard plasmid (not into a framework antibody vector). *See, e.g.*, FIG. 1(b). That the expression of the protein was conducted in E. coli, a prokaryotic host, does not address the absence of a library from which DNA is selected, as the present claims now require, or the absence of inserting DNA into a framework antibody vector. Thus Better et al. do not teach or fairly suggest all of the limitations of the presently claimed invention. Claim 12 has been canceled, but Applicants respectfully submit that Claim 2 is patentable for the reasons discussed above.

Applicants respectfully request withdrawal of the § 102 rejections based on the references discussed above.

The Examiner has also rejected Claims 1-17 under 35 U.S.C. § 102(b) as allegedly being anticipated by Wigler et al. (U.S. Patent 5,780,225). As discussed *supra*, Applicants filed a Petition to Revive a priority application, which, if granted, will place the priority date of the present application at January 11, 1990, effectively removing Wigler et al. as a prior art reference. Applicants thus respectfully request that the Examiner consider all other outstanding issues in the present application while awaiting a decision with respect to Applicants' Petition to Revive.

VIII. Double Patenting

The Examiner has also rejected Claims 1-17 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over Claims 2-11 of U.S. Patent No. 6,635,424. Applicants will submit a terminal disclaimer at such time as the obviousness-type double patenting rejection is the only outstanding rejection.

IX. Conclusion

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 2/13/07

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										>	109			118			127
										AGT	CAG	TCC	TTC	CCA	AAT	GTC	TTC
										Ser	Gln	Ser	Phe	Pro	Asn	Val	Phe
		136			145			154			163			172			181
CCC	CTC	GTC	TCC	TGC	GAG	AGC	CCC	CTG	TCT	GAT	AAG	AAT	CTG	GTG	GCC	ATG	GGC
Pro	Leu	Val	Ser	Cys	Glu	Ser	Pro	Leu	Ser	Asp	Lys	Asn	Leu	Val	Ala	MET	Gly
		190			199			208			217			226			235
TGC	CTA	GCC	CGG	GAC	TTC	CTG	CCC	AGC	ACC	ATT	TCC	TTC	ACC	TGG	AAC	TAC	CAG
Cys	Leu	Ala	Arg	Asp	Phe	Leu	Pro	Ser	Thr	Ile	Ser	Phe	Thr	Trp	Asn	Tyr	Gln
		244			253			262			271			280			289
AAC	AAC	ACT	GAA	GTC	ATC	CAG	GGT	ATC	AGA	ACC	TTC	CCA	ACA	CTG	AGG	ACA	GGG
Asn	Asn	Thr	Glu	Val	Ile	Gln	Gly	Ile	Arg	Thr	Phe	Pro	Thr	Leu	Arg	Thr	Gly
		298			307			316			325			334			343
GGC	AAG	TAC	CTA	GCC	ACC	TCG	CAG	GTG	TTG	CTG	TCT	CCC	AAG	AGC	ATC	CTT	GAA
Gly	Lys	Tyr	Leu	Ala	Thr	Ser	Gln	Val	Leu	Leu	Ser	Pro	Lys	Ser	Ile	Leu	Glu
		352			361			370			379			388			397
GGT	TCA	GAT	GAA	TAC	CTG	GTA	TGC	AAA	ATC	CAC	TAC	GGA	GGC	AAA	AAC	AGA	GAT
Gly	Ser	Asp	Glu	Tyr	Leu	Val	Cys	Lys	Ile	His	Tyr	Gly	Gly	Lys	Asn	Arg	Asp
		406			415	>											
CTG	CAT	GTG	CCC	ATT	CCA	G											
Leu	His	Val	Pro	Ile	Pro												

SEQ ID NO. 1

SEQ ID NO. 2

FIG. 4A

										>AGN	109 CAN	TCN Ser	TTN	118 CCN Pro	AAN	GTN Val	127 TTN
___ CCN Pro	___ CTN Leu	136 GTN Val	___ TCN Ser	___ TGN	145 GAN	___ AGN	___ CCN Pro	154 CTN Leu	___ TCN Ser	___ GAN	163 AAN	___ AAN	___ CTN Leu	172 GTN Val	___ GCN Ala	___ ATN	181 GCN Gly
___ TGN	___ CTN Leu	190 GCN Ala	___ CGN Arg	___ GAN	199 TTN	___ CTN Leu	___ CCN Pro	208 AGN	___ ACN Thr	___ ATN	217 TCN Ser	___ TTN	___ ACN Thr	226 TGN	___ AAN	___ TAN	235 CAN
___ AAN	___ AAN	244 ACN Thr	___ GAN	___ GTN Val	253 ATN	___ CAN	___ GGN Gly	262 ATN	___ AGN	___ ACN Thr	271 TTN	___ CCN Pro	___ ACN Thr	280 CTN Leu	___ AGN	___ ACN Thr	289 GGN Gly
___ GGN Gly	___ AAN	298 TAN	___ CTN Leu	___ GCN Ala	307 ACN Thr	___ TCN Ser	___ CAN	316 GTN Val	___ TTN	___ CTN Leu	325 TCN Ser	___ CCN Pro	___ AAN	334 AGN	___ ATN	___ CTN Leu	343 GAN
___ GGN Gly	___ TCN Ser	352 GAN	___ GAN	___ TAN	361 CTN Leu	___ GTN Val	___ TGN	370 AAN	___ ATN	___ CAN	379 TAN	___ GGN Gly	___ GGN Gly	388 AAN	___ AAN	___ AGN	397 GAN
___ CTN Leu	___ CAN	406 GTN Val	___ CCN Pro	___ ATN	415 CCN Pro	> G											

SEQ ID NO. 3
SEQ ID NO. 7

FIG. 4B

METHOD FOR GENERATING LIBRARIES OF ANTIBODY GENES COMPRISING AMPLIFICATION OF DIVERSE ANTIBODY DNA AND METHODS FOR USING THESE LIBRARIES FOR THE PRODUCTION OF DIVERSE ANTIGEN COMBINING MOLECULE

Wigler, et al.
Appl. No.: Unassigned Atty Docket: STRATAG.7C2DV2C1
REDLINE SHEET